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Original article

Incidence of malignant neoplasms and mortality in people affected by multiple sclerosis in the epoch of disease-modifying treatments: A population-based study on Tuscan residents

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ABSTRACT

Background: Conflicting data are currently available on the risk of malignancies in people affected by multiple sclerosis (pwMS), and the potential relative contribution to this risk of disease-modifying therapies (DMTs) is still debated. Moreover, data on the long-term prognosis of pwMS mostly derive from natural history studies and updated observations during the treatment era are lacking.

Methods: Incidence of cancer and mortality were analysed in a pwMS cohort of residents of Tuscany over a 17-year period of observation during the treatment era and compared with the rates observed in a 1:10 sex- and age-matched control population resident in the same geographical area.

Results: Six-hundred and sixty-one pwMS were included; median age 43 years (range 19–80); 87% affected by relapsing-remitting MS. Sixty-eight percent of the cases were exposed to DMTs over the study period. Age and sex standardized incidence of malignancy did not differ between the groups: 3.9 × 1000 (95% confidence interval, CI, 3.75–4.15) person-years and 4.1 × 1000 (95% CI 3.76–4.42) person-years in the MS and control cohorts, respectively. The most frequent cancers reported in pwMS were breast, gastrointestinal and gynaecological cancers. Standardized mortality rates were 2.0 × 1000 person-years (95% CI 1.58–2.37) and 2.4 × 1000 (95% CI 2.03–2.78) person-years in the MS and control cohorts, respectively, and did not differ between groups, also after excluding traumatic cause-of-death (1.6 vs 1.7).

Conclusions: The incidence of cancer and mortality did not differ between pwMS and the general population residing in the same geographical area, suggesting that life expectancy of pwMS has improved over the treatment era.

1. Introduction

Multiple Sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system affecting 2.5 million people worldwide and representing a relevant socio-economic burden (Thompson et al., 2018). MS has an uneven geographical distribution, and Italy is a high-prevalence country with more than 109,000 estimated prevalent patients in 2015 (Bezzini et al., 2016).

In the last two decades, various disease-modifying therapies (DMTs) have been approved for the treatment of MS, most of which exert their therapeutic effect through an immunomodulatory-immunosuppressive mechanism of action (Torkildsen et al., 2016). Current guidelines recommend that treatment with DMTs be established shortly after diagnosis of the disease, but no consensus exists on the proper timing of treatment discontinuation (Montalban et al., 2018). People affected by MS (pwMS) are therefore treated with DMTs for most of their lives after diagnosis, raising the question whether long-term exposure to these drugs might induce potential long-term serious adverse events. Conflicting data exist on whether long-term exposure to DMTs or MS diagnosis itself might affect the individual risk of developing neoplasms. It

Abbreviations: pwMS, people affected by multiple sclerosis; DMTs, disease-modifying therapies; CI, confidence interval.

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has been suggested that drugs with immunosuppressive effects might increase cancer risk in pwMS but no definite data on the actual risk of exposure to DMTs are available and factors that might contribute to cancer risk are rarely considered in these studies (Lebrun and Rocher, 2018). Establishing risks of malignancies in the MS population during treatment is therefore useful for long-term management of pwMS.

Despite potential concerns on long-term safety, the introduction of effective treatments for MS has undoubtedly improved the outcome and life expectancy of pwMS diagnosed in the treatment era, as supported by a reduction in standardized mortality ratios (SMRs, i.e. ratio of observed deaths in the study group to expected deaths in a reference population) from 3.1 for pwMS whose disease onset was in the period 1953–1974 to 0.7 for those diagnosed during 1997–2012 (Lunde et al., 2017). However, systematic evaluations of cause-specific mortality ratios are lacking, and ethnic and geographical area specificity of the MS population included in each study might limit the general validity of the results.

Therefore, we performed a population-based study aimed at assessing cancer incidence and mortality in pwMS who are residents in Tuscany, analysing a 17-year period over the treatment era. In this patient population, the incidence of all malignant cancers and all-cause and cause-specific mortality ratios were assessed and compared with a reference population resident in Tuscany in the same period.

2. Material and methods

Clinical and epidemiological data (date of birth, gender, MS form, date of the last follow-up and disability at last follow-up) of pwMS who had undergone a neurological evaluation at the Tuscan Region MS Referral Centre of the Careggi University Hospital in Florence (Italy) in the period 1 January 2002–31 December 2018 were retrospectively collected. Each patient was identified with a univocal anonymized code derived from the healthcare registration number, i.e. a unique personal identifier which is assigned when a person residing in Tuscany accesses the services of the Public Health System of Tuscany (Univocal Identification Number, IDUNI). This code, which is included in the Public Health registry, allows unambiguous identification of a patient in the registries and allows data to be obtained from the Tuscan health administrative database in an anonymized manner. PwMS were assigned with their personal IDUNI and anonymized data collected from clinical records were then handed to the Regional Health Agency, which provided patient information derived from administrative data sources.

Among pwMS in clinical follow-up at our centre in the above-mentioned period, only those diagnosed after 1 January 2002 and who had records in the registry up to 31 December 2018 or death were included in the study because of the availability of data. PwMS were classified according to the MS form at the last clinical follow-up, retrieved from clinical records; proportions of pwMS who presented a relapsing versus progressive onset were also provided. After identification of the patient population in the administrative dataset using IDUNI codes, information was collected from administrative data sources. The date of MS diagnosis was estimated adopting the date of either the first brain MRI or spinal tap recorded for each case, and a random control from clinical records was performed to assess the accuracy of this algorithm.

Life-course exposure to DMTs for each patient was estimated by the detection of at least two DMTs dispensations occurring on two distinct dates over the study period. All the following DMTs were considered: glatiramer-acetate (L03AX13), interferon beta-1A (L03AB07), interferon beta-1B (L03AB08); di-methyl fumarate (N07XX09), pegylated interferon beta-1A (L03AB13), teriflunomide (L04AA31), fingolimod (L04AA27), natalizumab (L04AA23), alemtuzumab (L04AA34), cladribine (L01BB04), ocrelizumab (ATC code: L04AA36), rituximab (L01XC02), mitoxantrone (L01DB07), azathioprine (L04AX01), cyclophosphamide (L01AA01). Disability was estimated using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) detected at the last clinical follow-up. Progression index (PI) was then calculated as a ratio of EDSS and disease duration (since MS diagnosis, expressed in years) at last follow-up. To explore potential correlations between PI and the outcomes (cancer incidence and mortality), a stratification of pwMS according to the corresponding quartile of PI was performed.

People not affected by MS registered in the public health registry who were alive and residing in Tuscany from 1 January 2002 to 31 December 2018, or death, were included as a potential control cohort. A 1:10 case-control matching for sex and age (according to five-year epochs of age) was then performed to select the control population included in the study. Controls were age-matched to cases adopting age at MS diagnosis, therefore age at the beginning of observation was similar between the two cohorts.

Incident cases of cancer were identified from hospital discharge records, selecting the diagnosis discharge codes 140*−208*, according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) (International Classification of Diseases 2020). Only those events occurring after the date of MS diagnosis were considered. In the incidence analysis, individuals who had been hospitalised with a diagnosis of cancer in the five years prior to the observation period were excluded in order to properly explore new incident diagnoses of neoplasms.

Mortality was estimated from the inhabitant registry, which provides data regarding date of death and cause of death (COD), encoded with ICD9-CM classification. For the analysis of COD, we adopted the underlying COD, defined as “the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury” (Prevention CfDCa 2021). Information on COD was available for deaths that occurred until 31 December 2016 and therefore analysis of the incidence of mortality was applied to the period 1 January 2002−31 December 2016.

2.1. Outcomes

The aim of this study was to estimate the incidence of cancer and mortality in a MS cohort residing in Tuscany and to compare it with the rates observed in an age- and sex-matched control cohort residing in the same geographical area. The incidence rate was calculated both as crude rate and as rate standardized by age and sex, thus allowing comparison of the results in the two groups adjusting further for the differences in these variables. The 95% confidence interval (CI) was reported as a measurement of the effect size of sex and age. Mortality was reported according to the main COD and categorized into traumatic-related COD and non-traumatic COD; the latter category encompasses the following: cancer, cardiovascular diseases, respiratory diseases and infections.

2.2. Statistical analysis

The incidence rates of cancer or death were calculated by dividing the number of observed cases by person-years. The estimates were reported in rates per 1000 residents associated with their relative CI. For each patient, the person-years was calculated as the sum of number of days between the diagnosis date and failure event. The incidence rates were standardized for sex and age. The standard population used was that of the residents in Tuscany on 1 January 2011. The incidence rates (crude and standardized) were stratified for PI. Mortality was stratified for traumatic- and non-traumatic COD. All statistical analyses were performed by STATA software, version 14.

Continuous variables are reported as median value and range. Comparisons were performed with non parametric tests, as appropriate according to the distribution of data. Age at the mid-point of observation in the study (i.e. the middle timepoint between diagnosis and 31 December 2018 or death) was calculated using each individual’s date of birth and the year corresponding to the mid-point of the observation period for the same individual. For example, if a subject was born in 1970 and the observation period of the study was from 2005 (year of MS diagnosis) to 2017, the age at the mid-point of observation would be:

2005 + (2017–2005)/2–1970 = 41 years.

3. Results

3.1. Patient and control inclusion and characteristics

Among individuals who underwent neurological evaluation at our centre in the study period, 1708 pwMS were identified; 645 patients were excluded from the analysis because they were not residents in Tuscany and 89 because of missing data. Out of 974 cases, 313 pwMS who were diagnosed before 1 January 2002 were excluded from the analysis due to a lack of consistent data and the remaining 661 pwMS who had records in the registries up to 31 December 2018 or death were included in the study (Fig. 1).

Baseline clinical and demographic characteristics of the included patients are reported in Table 1. There were 452 females (68%) and 209 males; the median age at MS diagnosis (corresponding to age at inclusion in the study) was 37 years (range 14–80), and at the mid-point of observation in the study 32% of the cases were between 36 and 45 years of age. A relapsing onset was observed in 647 out of 661 (98%) pwMS included, and most of the cases (87%) were affected by relapsing-remitting (RR-) MS at the last clinical follow-up. The mean follow-up duration was nine years. At last follow-up at our centre, disability was low (i.e. EDSS $\leq$2) in 425 pwMS (64%), moderate (EDSS between 4.0 and 6.0 included) in 111 cases (17%) and severe (EDSS $\geq$6.5) in 51 cases (8%). Sixty-eight percent of the patients had been exposed to DMTs over the study period.

With regard to the control population, 6610 individuals were included: 4520 females (68%) and 2090 males (32%). The median age at study entry was 37.6 years (range 14–81), whereas it was 43 years at the mid-point of observation.

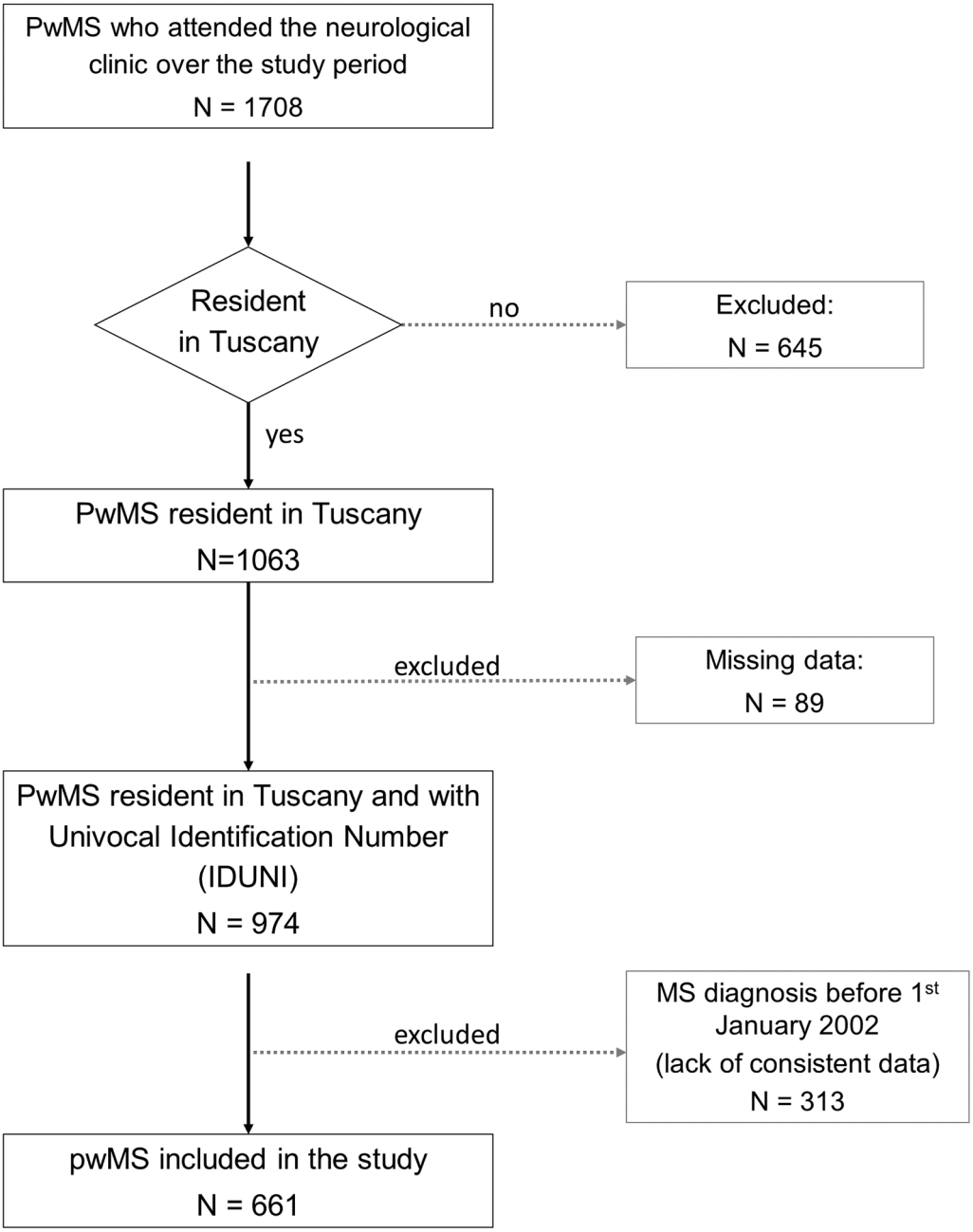

Fig. 1. Flow diagram for patient inclusion.

Table 1
Baseline clinical and demographic characteristics of the patient population included, reported for the overall cohort (all MS) and according to the form of MS detected at the last clinical follow-up.

Variable	All MS $n = 661$	RR-MS $N = 574$ (87%)	SP-MS $N = 73$ (11%)	PP-MS $N = 14$ (2%)
Gender female, *n* (%)	452 (68%)	400 (70%)	49 (67%)	3 (21%)
Age at MS diagnosis (and inclusion in the study), median (range)	37 (14–80)	36 (14–73)	46 (14–80)	43 (35–74)
Age at the mid-point of observation, years, median (range)	43 (19–80)	40 (19–75)	51 (20–80)	48 (39–78)
Age at the end of observation, years, median (range)	46 (21–83)	45 (21–80)	55 (26–81)	53 (43–83)
EDSS at last follow-up, median (range)	2.7 (0.0–9.0)	1.7 (0.0–8.0)	6.2 (2.5–9.0)	5.4 (1.5–7.5)
Disease duration at last follow-up, years, median (range)	6.6 (1–17)	6.4 (1–17)	7.7 (1–16)	7.8 (2–14)
MS cases exposed to DMTs, *n* (%)	453 (68%)	402 (70%)	46 (63%)	5 (36%)

DMTs, disease-modifying treatments; EDSS, expanded disability status scale; MS, multiple sclerosis; *N*, number; RR-, relapsing-remitting; PP-, primary progressive; SP-, secondary progressive.

3.2. Incidence of malignant cancer

In the MS cohort, 23 cases of malignancy were observed over 5746 person-years of observation, with a crude incidence rate of 4.0 × 1000 person-years and a standardized incidence rate of 3.9 × 1000 (95% CI 3.75–4.15) person-years. In the control cohort, 265 cases of malignant cancer were reported over 61,675 person-years of observation, thus corresponding to a crude incidence rate and a standardized rate of 4.3 × 1000 person-years and 4.1 × 1000 (95% CI 3.76–4.42) person-years, respectively. No differences were detected in global cancer incidence between pwMS and the reference population (95% CI overlapping). The median age at cancer diagnosis was 52 years (27–71) in the MS cohort, 51 years (27–71) in the RR-MS subgroup, and 63 years (63–70) in the secondary-progressive (SP-) MS subgroup (0 cases detected in primary-progressive, PP-, MS patients). The median age at cancer diagnosis was 57 years (range 24–73) in the control cohort and it did not differ from that of the MS cohort ($p = 0.123$). Twenty out of 23 individuals (87%) who received a diagnosis of malignant cancer were females. The most frequent cancers reported were breast cancers (six cases), followed by gastrointestinal and gynaecological cancers (five cases each), accounting collectively for 70% of the cases. The remaining malignancies were the following: lung cancers (three cases), thyroid cancers (two cases), urinary and prostate cancer (one case each). Incidence of cancer varied across different PI quartiles without a trend, ranging from 2.5 × 1000 person-years in pwMS in the fourth quartile (i.e. ≥0.7) to 5.1 × 1000 person-years for pwMS in the second quartile of PI (i.e. 0.3–0.4). In the control group, the most frequent malignancy observed was breast cancer (71 cases, 27%), followed by urinary tract cancers (65 cases, 24%) and prostate cancer (52 cases, 20%). Detailed information on the frequency and type of neoplasms is summarized in Table 2.

3.3. Mortality

Incidence of mortality was analysed over the period 1 January 2002–31 December 2016, according to availability of source data. In the MS cohort, 10 deaths were reported over 4543 person-years of observation, thus accounting for a crude mortality rate of 2.2 × 1000 person-years and a standardized mortality rate of 2.0 × 1000 person-years (95% CI 1.58–2.37). Five out of 11 cases (45%) were males and four out of 11 cases (36%) were affected by progressive MS (twoPP-, and two SP-MS). Two trauma-related deaths were observed in pwMS; the remaining COD are detailed in Table 3.

Table 2
Malignant cancers observed in the MS and control cohorts.

	MS cohort *n* of cases (frequency)	Control cohort *n* of cases (frequency)
Breast	6 (26%)	71 (27%)
Digestive	5 (22%)	46 (17%)
Gynaecological	5 (22%)	12 (4%)
Endocrine	2 (9%)	5 (2%)
Prostate	1 (4%)	52 (20%)
Respiratory	3 (13%)	12 (5%)
Urinary	1 (4%)	65 (24%)
Skin	0 (0%)	1 (0.5%)
Haematological	0 (0%)	1 (0.5%)
Total	23	265

Standardized non-traumatic mortality was 1.6 × 1000 person-years (95% CI 1.36–1.98). In the control cohort, 127 deaths were reported over 49,122 person-years of observation; crude and standardized mortality rates were 2.6 × 1000 person-years and 2.4 × 1000 (95% CI 2.03–2.78) person-years, respectively. Thirty-two out of 127 deaths (25%) were related to a traumatic cause; the remaining CODs are detailed in Table 3. Excluding traumatic COD, crude and standardized rates were 1.9 × 1000 person-years and 1.7 × 1000 (95% CI 1.18–2.20) person-years, respectively. Non-traumatic mortality did not differ between pwMS and the reference population. The median age at death was 69 years (34–83) in the MS cohort and 64 years (31–85) in the control cohort, the difference not being significant ($p = 0.104$). Mortality was high in pwMS with the highest quartile of progression index (mortality rate of 5.1 × 1000 person-years for PI ≥ 0.7), low (0.8 × 1000 person-years) for progression index 0.3–0.6, and intermediate (2.3 × 1000 person-years) for cases with low progression index (0.1–0.2).

4. Discussion

In the present study, the incidence of cancer and mortality was analysed in an MS population residing in Tuscany over a 17-year period during the treatment era, and it was compared to that observed in a 1:10 age- and sex-matched control cohort of individuals residing in the same geographical area. PwMS who had undergone a neurological evaluation at the MS clinic over the study period (1 January 2002–31 December 2018) were first identified from the clinical records of the MS centre; the corresponding anonymized codes that univocally identify individuals who had accessed the healthcare system (IDUNI) were then adopted to collect information from administrative data sources using pre-defined algorithms. As previously reported, the adoption of administrative data sources to obtain valid information for population-based studies in MS, managing data in an anonymized manner using univocal

Table 3
Causes of death in the MS and control cohorts.

Cause of death	MS cohort *n* (frequency)	Control cohort *n* (frequency)
Multiple sclerosis	3 (30%)	—
Trauma	2 (20%)	32 (25%)
Malignant neoplasm	3 (30%)	60 (47%)
Cardiovascular disease	0 (0%)	11 (9%)
Cerebrovascular disease	0 (0%)	8 (6%)
Not neoplastic gastrointestinal disorder	0 (0%)	6 (5%)
Acute kidney failure	1 (10%)	0 (0%)
Sepsis	0 (0%)	4 (3%)
Diabetes	0 (0%)	2 (2%)
Obesity	0 (0%)	2 (2%)
Alzheimer disease	0 (0%)	2 (2%)
Missing	1 (10%)	0 (0%)
Total cases	10	127

identification codes, allows the collection of data in a cost-effective, economic, and standardized way (Bezzini et al., 2018). However, the quality of the data provided from administrative data sources may only be moderate, as specific clinical information or information related to services that are not provided by the Italian Health Service might be missing. To partially overcome this issue, in the present study administrative data were implemented with information obtained from clinical records held at the neurological clinic, and identification of the individuals affected by MS included in the study was undertaken using clinical records rather than applying a case-finding algorithm to administrative data (Bezzini et al., 2016). After excluding patients who were not residents in Tuscany and those for whom clinical information was not available, 661 pwMS were included in the study. The demographical characteristics of the MS cohort were aligned with the epidemiology of the disease, suggesting that this cohort is representative of a general MS population (Leray et al., 2016).

The sex- and age-standardized incidence of malignant cancer in the MS cohort did not differ from that observed in the control cohort, suggesting that MS diagnosis did not increase the risk of cancer in the population included in the present study. This observation is consistent with previous findings from two population-based disease registers, the Danish Cancer Register and the Danish Multiple Sclerosis Register, where the risk of malignancies was not increased in pwMS compared to the general population (Nielsen et al., 2006). These data were confirmed by a recent analysis of the Danish MS cohort evaluating pwMS who were selected for having received MS diagnosis in the years 1995–2015, i.e. following the introduction of DMTs (Norgaard et al., 2019). However, the exposure to DMTs was not specifically evaluated in the latter study, although it was speculated from indirect evidence that around one-third of the patients would likely have received DMTs at one point during the study period.

No univocal data are available for now on the potential impact of DMTs on cancer risk in pwMS. A study of cause-specific mortality in pwMS from the North America Research Committee on Multiple Sclerosis (NARCOMS) registry reported that participants aged 25–54 years had a higher proportion of deaths from cancer than expected, and according to the Authors these data could suggest earlier unmasking of cancer due to drug therapy or treatment-related cancers (Cutter et al., 2015). However, as the Authors acknowledged themselves, treatment-related factors were not examined in the study, therefore the potential contribution of DMTs to the observed increased cancer-related mortality could not be properly estimated. A potential role of DMTs in cancer risk was suggested by an Italian cohort study reporting that more than two switches of DMTs were associated with a higher risk of developing cancer in a multivariate analysis, where also age, age at MS onset, and disease duration were significantly associated with cancer risk (D'Amico et al., 2019). Given the known differences in mechanisms of action amongst DMTs, it can be speculated that each class of DMT might exert a potentially different impact on the risk of developing malignancies, if any. Exposure to immunomodulators does not seem to increase cancer risk in pwMS, but an increased risk was associated with long-term immunosuppressive treatments (Lebrun and Rocher, 2018). More recently, a nationwide register-based study in Sweden including 6136 pwMS treated with fingolimod, natalizumab or rituximab did not show an increase in the risk of invasive cancer with rituximab and natalizumab compared to the general population; however, a borderline-significant increased risk with fingolimod compared to both the general population and rituximab was observed (Alping et al., 2020).

In the present study, two-thirds of pwMS had actually received DMTs over the observation period, but no conclusive data on treatment-related risk of cancer can be provided as the duration of the treatment was not estimated for each DMT because DMTs exposure analysis was beyond the aim of the study. Moreover, the exposure time to the treatments might be too short to enhance a potential cancer risk, and the study could be underpowered for this purpose, considering that treated patients were receiving different DMTs and untreated patients were also included.

When analysing organ-specificity of the malignancies reported, breast cancers were the most frequently observed in both pwMS and the reference population, as expected considering the epidemiological characteristics of the cases included (Ferlay et al., 2018), but no differences in incidence were reported between the two groups. A higher incidence of gastrointestinal and gynaecological cancers was observed in pwMS compared to the reference population; however, the relatively small sample size prevented us from drawing any conclusions, and further studies on larger populations are needed to ascertain whether pwMS show an increased risk of organ-specific cancers. These data are aligned with previous observations from a systematic review on the incidence and prevalence of cancer in MS, analysing 38 studies conducted in the period 1953–2010 (Marrie et al., 2015); cervical, breast, and digestive cancers were the most frequent malignancies reported in this work. Increased incidence of other organ-specific cancers was described, such as bladder cancer, in a population-based study in Ontario (Marrie et al., 2021), and melanoma skin cancer in a Danish study (Norgaard et al., 2019). The increased risk of different organ-specific cancers detected across studies suggests a relevant contribution to this risk of genetic and environmental co-factors specific for the study population; this suggests that caution should be adopted in generalizing such observations to pwMS residing in different geographical areas and with different genetic background.

Overall mortality was lower in pwMS compared to the reference population, but this somehow surprising data can be explained, at least in part, considering that traumatic events account for the most frequent COD in a reference population of young adults, while pwMS might be partially protected from traumatic COD due to lifestyle modifications induced by the disease. After excluding traumatic COD from the analysis, standardized mortality rates did not differ between the two cohorts. These data are aligned with the results of a longitudinal population study in Norway reporting a significant reduction in SMRs over time, and showing a SMR of 0.7 for cases with disease onset in the period 1997–2012 (Lunde et al., 2017). Moreover, a population-based study in Denmark reported a gradual reduction in SMRs and an increase in age at death over subsequent decades in the period 1950–2009, being the age at death for those deceased over the period 2000–2009 similar to that observed in the present study (64 and 65.4 years, respectively) (; Koch-Henriksen et al., 2017). These observations suggest overall an improvement in life expectancy of pwMS compared to what has previously been reported by natural history studies, where life expectancy was reduced in pwMS compared to the general population (Scalfari et al., 2013).

In this study, MS represented about 30% of the COD, a rate similar to that observed in a study with a similar observation period (1997–2009) (Lalmohamed et al., 2012), whereas rates as high as 60% were previously reported in longitudinal studies performed in different epochs, with observation periods starting, for the most part, in the 1940s and 50s (Scalfari et al., 2013). As already pointed out by other Authors (Scalfari et al., 2013), such differences could be due to multiple factors, such as the methods adopted for the individuation of COD, the clinical-demographic characteristics of the study population, and the epoch of observation. This latter variable might account for changes in both the diagnostic criteria of MS (inclusion of higher proportions of "benign cases" in more recent studies than in earlier ones) and the provision of DMTs and supportive care (Grytten, 2017), with subsequent improvement in the quality of life and MS-related disability (Harding et al., 2020). The reduction in MS COD is consistent with the observation of standardized mortality rates similar between the MS population and the control cohort, suggesting that in this study the diagnosis of MS is not associated with increased risk of death. Exposure to treatment probably contributed to this phenomenon, as two-thirds of the pwMS had been exposed to DMTs during the observation period. However, also the inclusion of a young population with low-moderate disability and relatively short follow-up might, at least in part, account for these

findings. Moreover, the PP-MS form, which is associated with higher SMRs (Lunde et al., 2017; Kingwell et al., 2012), was under-represented in this population. An excess of mortality was indeed detected in pwMS with a high progression index compared to those with a low progression index, identifying a subset of cases affected by rapidly evolving disease and harbouring a poor prognosis. This is in agreement with the observation that infections are common concurrent COD in MS, as these are typically associated with advanced disability and immobility (Harding et al., 2020).

Our study has, however, several limitations. First of all, caution is required in the overall interpretation of the results due to the relatively small sample size of the study and low incidence of the events examined, and studies in larger cohorts are required to confirm these findings. A selection bias might derive from the inclusion of pwMS who had performed at least one on-site visit in the neurological clinic over a defined period, thus potentially excluding highly disabled patients who are home-ridden and do not routinely attend the clinics. Controls were followed on average for six months longer than cases, therefore a potential underestimation of incidence of cancer in the MS cohort cannot be excluded, although it seems unlikely to explain an excess of cancers occurring in the MS group masked by this difference. As in other population-based studies, correction for potential confounders (e.g. risk factors for cancer and mortality) could not be performed due to a lack of source data. As previously stated, the impact of specific DMTs on cancer risk could not be explored because treatment duration was not estimated, as DMTs exposure analysis was beyond the scope of the present study. A more detailed analysis of COD risk and SIRs for each cancer type was not performed due to the small number of incident cases which did not allow us to perform a multivariate analysis.

5. Conclusions

This population-based study has shown that incidence of cancer and mortality did not differ between pwMS and the general population residing in the same geographical area analysed over a 17-year period of observation during the treatment era. These data suggest that the natural history of MS has improved over the last two decades, probably thanks to early diagnosis, proper management of complications, and availability of effective DMTs. No differences in the incidence of malignancies compared to the reference population were observed, but further studies investigating long-term cancer risk on larger cohortsaccording to exposure to DTMs and controlling for known cancer risk factors are required to properly explore this issue.

Declarations

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Availability of data and material (data transparency): Anonymized and aggregated data are available from the corresponding author on reasonable request.

Code availability: not applicable.

Ethics approval: ethics approval for the conduction of the present study was not required because the Tuscany Regional Health Agency is authorized to manage de-identified and anonymized data of patients attending the neurological clinic of the University Hospital of Careggi, as data are processed in full compliance with the privacy regulation in an anonymized manner by the adoption of the Univocal Identification Number (IDUNI) code.

Consent to participate (include appropriate statements): not applicable

Consent for publication (include appropriate statements): not applicable

CRediT authorship contribution statement

Alice Mariottini: Data curation, Writing – original draft, Conceptualization. **Benedetta Forci:** Conceptualization, Data curation, Investigation, Writing – original draft. **Elisa Gualdani:** Data curation, Formal analysis, Visualization, Writing – original draft. **Monica Romoli:** Resources, Data curation. **Anna Maria Repice:** Investigation, Resources. **Alessandro Barilaro:** Investigation, Resources. **Claudia Mechi:** Investigation, Resources. **Luca Massacesi:** Conceptualization, Investigation, Writing – review & editing, Supervision. **Paolo Francesconi:** Conceptualization, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

A. Mariottini reports non-financial support from Biogen idec, Sanofi Genzyme, Novartis, Teva, Roche, and personal fees from Merck Serono and Sanofi Genzyme, outside the submitted work;

B. Forci reports no disclosures relevant to the manuscript;

E. Gualdani reports no disclosures relevant to the manuscript;

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